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Allergen specificity of early peanut consumption and effect on development of allergic disease in the Learning Early About Peanut Allergy study cohort

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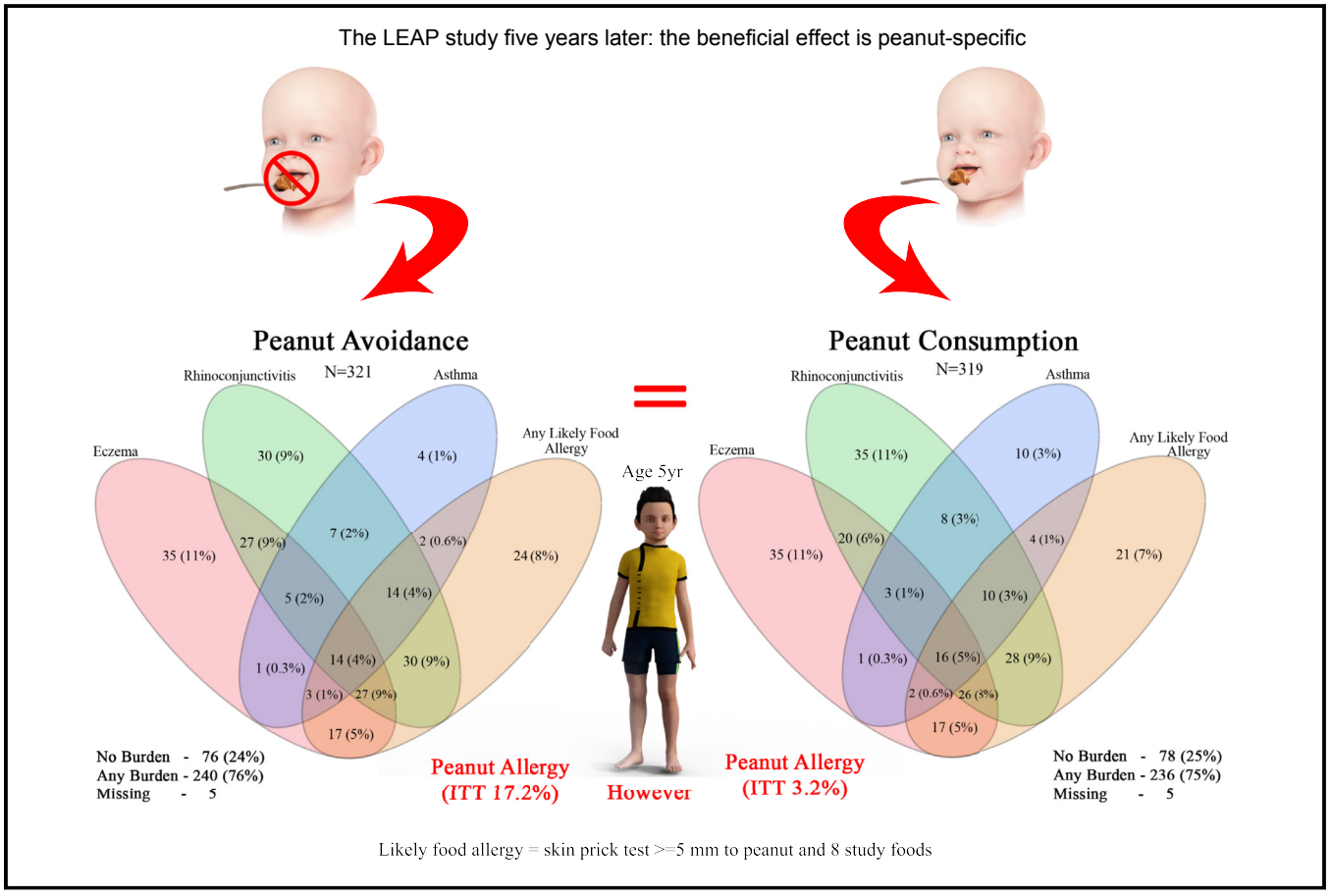
GRAPHICAL ABSTRACT



Background: Early introduction of dietary peanut in high-risk infants with severe eczema, egg allergy, or both prevented peanut allergy at 5 years of age in the Learning Early About Peanut Allergy (LEAP) study. The protective effect persisted after 12 months of avoiding peanuts in the 12-month extension of the LEAP study (LEAP-On). It is unclear whether this benefit is allergen and allergic disease specific.

Objective: We sought to assess the effect of early introduction of peanut on the development of allergic disease, food sensitization, and aeroallergen sensitization.

Methods: Asthma, eczema, and rhinoconjunctivitis were diagnosed based on clinical assessment. Reported allergic reactions and consumption of tree nuts and sesame were recorded by questionnaire. Sensitization to food allergens and

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aeroallergens was determined by means of skin prick testing and specific IgE measurement.
Results: A high and increasing burden of food allergen and aeroallergen sensitization and allergic disease was noted across study time points; 76% of LEAP participants had at least 1 allergic disease at 60 months of age. There were no differences in allergic disease between LEAP groups. There were small differences in sensitization and reported allergic reactions for select tree nuts, with levels being higher in the LEAP consumption group. Significant resolution of eczema and sensitization to egg and milk occurred in LEAP participants and was not affected by peanut consumption.
Conclusion: Early consumption of peanut in infants at high risk of peanut allergy is allergen specific and does not prevent the development of other allergic disease, sensitization to other food allergens and aeroallergens, or reported allergic reactions to tree nuts and sesame. Furthermore, peanut consumption does not hasten the resolution of eczema or egg allergy. (J Allergy Clin Immunol 2018;141:1343-53.)

Key words: *Food allergy, peanut allergy, allergy prevention, allergen-specific asthma, eczema, atopic dermatitis, rhinoconjunctivitis, tolerance*

Abbreviations used
ITT: Intention-to-treat
LEAP: Learning Early About Peanut Allergy
LEAP-On: Twelve-month extension of the LEAP study (Persistence of Oral Tolerance to Peanut)
PP: Per-protocol
SPT: Skin prick test

Atopic diseases represent a public health concern, particularly in the developed world.[1-3] Atopic conditions rarely occur in isolation, and children frequently have multiple allergic diseases. For example, infants with eczema are at higher risk of food allergy and asthma, children with egg allergy are at increased risk of allergic respiratory diseases, and children with a single food allergy frequently have additional food allergies.[3]

Early dietary allergen exposure has been shown to be a successful strategy for the prevention of peanut allergy (and possibly egg allergy); however, the specificity of the observed clinical and immunologic benefits is not known.[4-10] Peanuts, tree nuts, and sesame contain seed storage proteins with highly conserved areas of shared identity and homology between their amino acid sequences.[11-13] This raises the important clinical question of whether cross-sensitization to similar allergens accounts for the frequent co-occurrence of these allergies in allergic populations.

If the consumption of peanut during infancy protects against the development of peanut allergy, it might also protect against the development of related food allergies. Israeli children have a low prevalence of peanut, tree nut, and sesame allergy when compared with age-matched UK children.[14] Israeli children consume high quantities of both peanut and sesame from an early age, which is likely to explain the difference in peanut and sesame allergy rates.[14,15] However, the differences in tree nut allergy cannot be attributed to early tree nut consumption because there were no differences in the age at which tree nuts were introduced between the 2 countries. Thus the low levels of tree nut allergy might be the result of cross-tolerance induced through earlier, greater, and more frequent consumption of peanut, sesame, or both in Israel compared with the United Kingdom.

Given the possible clinical relevance of cross-reactivities between proteins in different foods and given that there is low-grade evidence that allergen immunotherapy can prevent new-onset aeroallergen sensitization,[16,17] it is reasonable to investigate whether early dietary allergen exposure has an influence on the onset or resolution of coexistent food allergies, other atopic diseases, or both.

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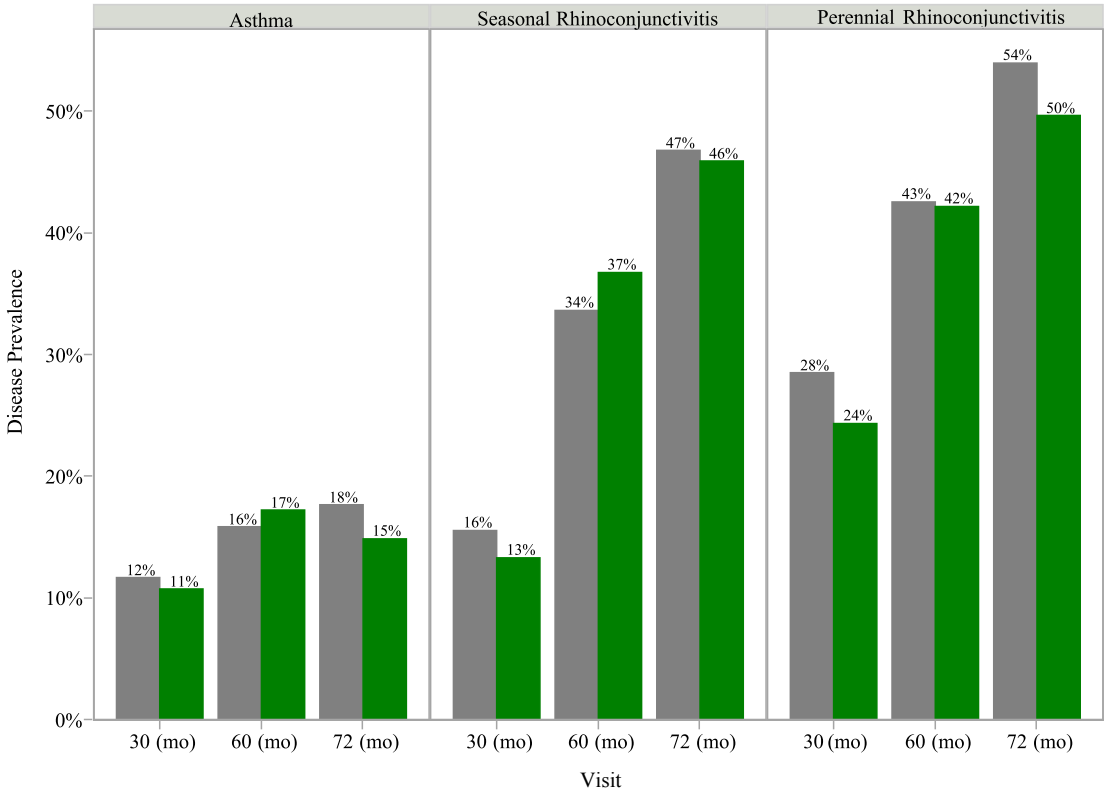

FIG 1. Asthma and rhinoconjunctivitis burden over time. Rates of protocol-defined asthma, seasonal rhinoconjunctivitis, and perennial rhinoconjunctivitis in the consumption *(green bars)* and avoidance *(gray bars)* groups in the ITT population at 30, 60, and 72 months of age are shown. There are no significant differences between the 2 groups at any time point, as assessed by using χ^2 tests.

METHODS

Study design

This is an *a priori* analysis of the Learning Early About Peanut Allergy (LEAP) and the 12-month extension of the LEAP study (LEAP-On study) on secondary allergic outcomes.[10,18] The LEAP study was a randomized, open-label, controlled trial comparing 2 strategies to prevent peanut allergy: consumption or avoidance of peanut by high-risk infants until 60 months of age. The LEAP-On study was a 2-sample comparison using all evaluable study participants from the LEAP study assessed at 72 months of age after 12 months of peanut avoidance. Both trials were approved by the institutional review board and were overseen by a National Institute of Allergy and Infectious Diseases Allergy and Asthma Data and Safety Monitoring Board. Written informed consent was obtained for all LEAP and LEAP-On participants from their parent/guardian; full study details have been published previously.

Enrollment and study procedures

The LEAP study enrolled infants aged at least 4 months and less than 11 months with severe eczema, egg allergy, or both from December 2006 to May 2009.[10] Participants were stratified at baseline into 2 separate study populations (strata) based on skin prick test (SPT) results for peanut and then randomly assigned to avoid (LEAP avoiders) or consume (LEAP consumers) peanut. The analysis in this article combines data from both the SPT-positive and SPT-negative strata. Participants randomly assigned to consumption were fed at least 6 g of peanut protein per week until age 60 months. Clinical assessments were undertaken at baseline (age 4-11 months) and at the ages of 12, 30, and 60 months, which included determination of protocol-defined eczema, asthma, and seasonal and perennial rhinoconjunctivitis, which are further detailed in the text in this article's Online Repository at www.jacionline.org). The LEAP-On clinical assessment was undertaken at 72 months of age after 12 months of peanut avoidance in both groups.[18]

SPTs and specific IgE measurement

Immune assessments, including SPTs and specific IgE measurements, were conducted; test methodologies and SPT materials have been published previously.[10] SPT responses to food allergens (peanut, hen's egg white [using standardized extract and prick-prick testing with raw hen's egg white], cow's milk, sesame, and soya) were assessed at baseline and 12, 30, and 60 months of age (ALK-Abelló, Hørsholm, Denmark). SPTs to all allergens except soya were repeated at 72 months of age. At 60 and 72 months, Brazil nut, hazelnut, cashew, walnut, and almond were also included. Levels of allergen-specific IgE to peanut, hen's egg white, cow's milk, sesame, Brazil nut, hazelnut, cashew, walnut, and almond were measured at screening and 12, 30, 60, and 72 months of age by using ImmunoCAP (Thermo Fisher, Uppsala, Sweden). Levels of specific IgE to the aeroallergens house dust mite, cat, dog, timothy grass pollen, birch pollen, and *Alternaria* species mold were measured at 30, 60, and 72 months of age (Thermo Fisher).

Mean SPT responses and specific IgE values were calculated for the above allergens at all available time points; these means are presented for the intention-to-treat (ITT) and per-protocol (PP) study populations. We defined sensitization *a priori* for food allergens as an SPT wheal diameter of 3 mm or greater or a specific IgE level of 0.35 kU/L or greater and for aeroallergens as a specific IgE level of 0.35 kU/L or greater. Based on previous publications and on the optimal predictive value for participants with peanut allergy in the avoidance arm of LEAP (see this article's Online Repository at www.jacionline.org), we made use of high-level cutoffs of SPT wheal diameters of 5 mm or greater and/or specific IgE levels of 10 kU/L or greater to define "likely food allergy" in *post hoc* analyses.[19]

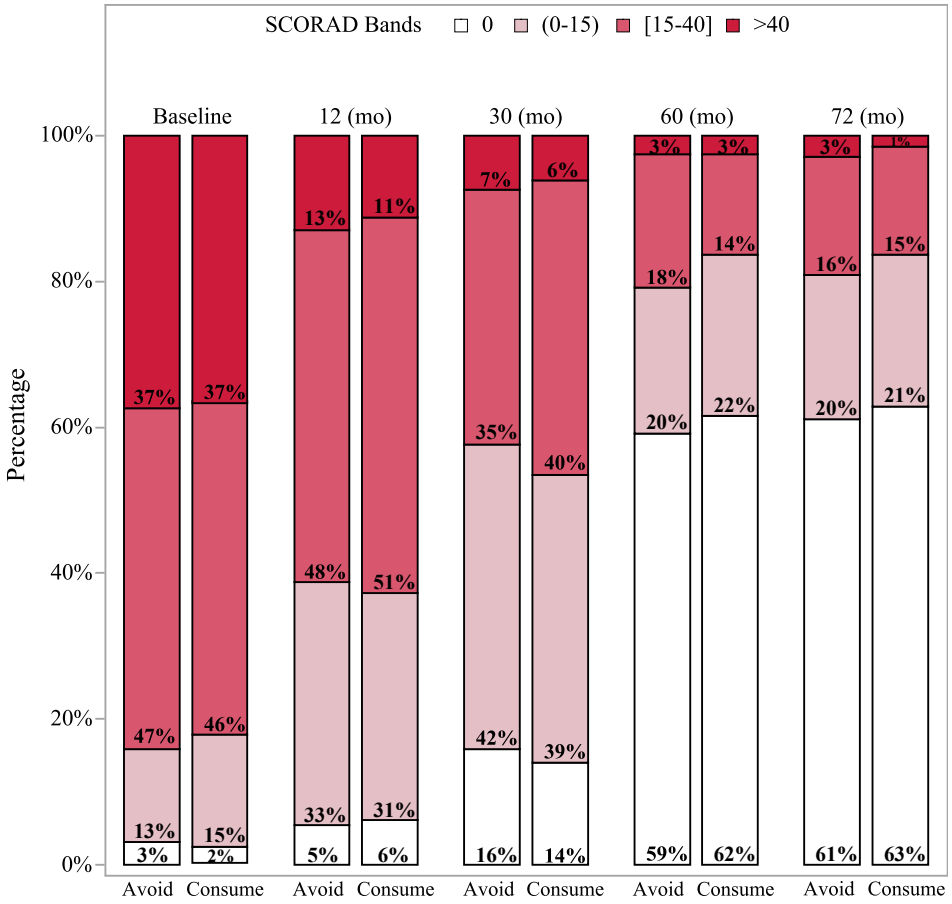

FIG 2. Eczema severity bands over time (SCORAD). Percentage of subjects with SCORAD assessments for eczema of 0, greater than 0 to 15, 15 or greater to 40, and greater than 40 are shown at baseline and at 12, 30, 60, and 72 months in the avoidance (*left bar* of each pair) and consumption (*right bar* of each pair) groups in the ITT population. There are no significant differences between the 2 groups at any time point, as assessed by using χ^2 tests.

Reported allergic reactions and association with specific IgE sensitization

At 60 months of age, a study questionnaire recorded details of suspected allergic reactions that occurred over the duration of the trial. Two-by-two comparisons were made comparing tree nut and sesame-induced reported allergic reactions and specific IgE levels of 0.35 kU/L or greater to each allergen.

Consumption of tree nuts and sesame

Participant-reported consumption of Brazil nut, hazelnut, cashew, walnut, almond, or sesame on at least 1 occasion was assessed from 3-day food diaries completed at 6 study time points.

Statistical analysis

Statistical analyses were performed on all LEAP and LEAP-On study participants for whom an outcome measurement was obtained on an ITT basis comparing the 2 randomized treatment groups cross-sectionally. Analyses were also performed on those who met the PP criteria for the LEAP study (details of which have been published previously). Fisher exact tests, χ^2 tests, or multivariate logistic regression were used to compare the proportion of participants with each disease outcome of interest at the .05 level of significance. These were planned analyses on secondary outcomes, and no adjustments have been made for multiple comparisons. All analyses were performed with SAS software, version 9.4, or JMP, version 12 (SAS Institute, Cary, NC). Datasets for the analyses are available through TrialShare, a public Web site managed by the Immune Tolerance Network (https://www.itntrialshare.org/LEAPON_JACI_2017.url).

RESULTS

Participants

The characteristics of participants screened and enrolled in the LEAP and LEAP-On studies have been published previously.[10,18]

No difference in development of allergic disease between LEAP study intervention groups

No differences were noted between LEAP avoiders and consumers in the rate of asthma, seasonal rhinoconjunctivitis, and perennial rhinoconjunctivitis at 30, 60, and 72 months of age in the ITT population (Fig 1 and Table E1 in this article's Online Repository at www.jacionline.org). These findings were replicated in the PP population (Table E2). Additionally, there were no differences in eczema between the 2 LEAP avoiders and consumers at any study visit in the ITT (Fig 2 and Table E3) and PP populations (Table E4).

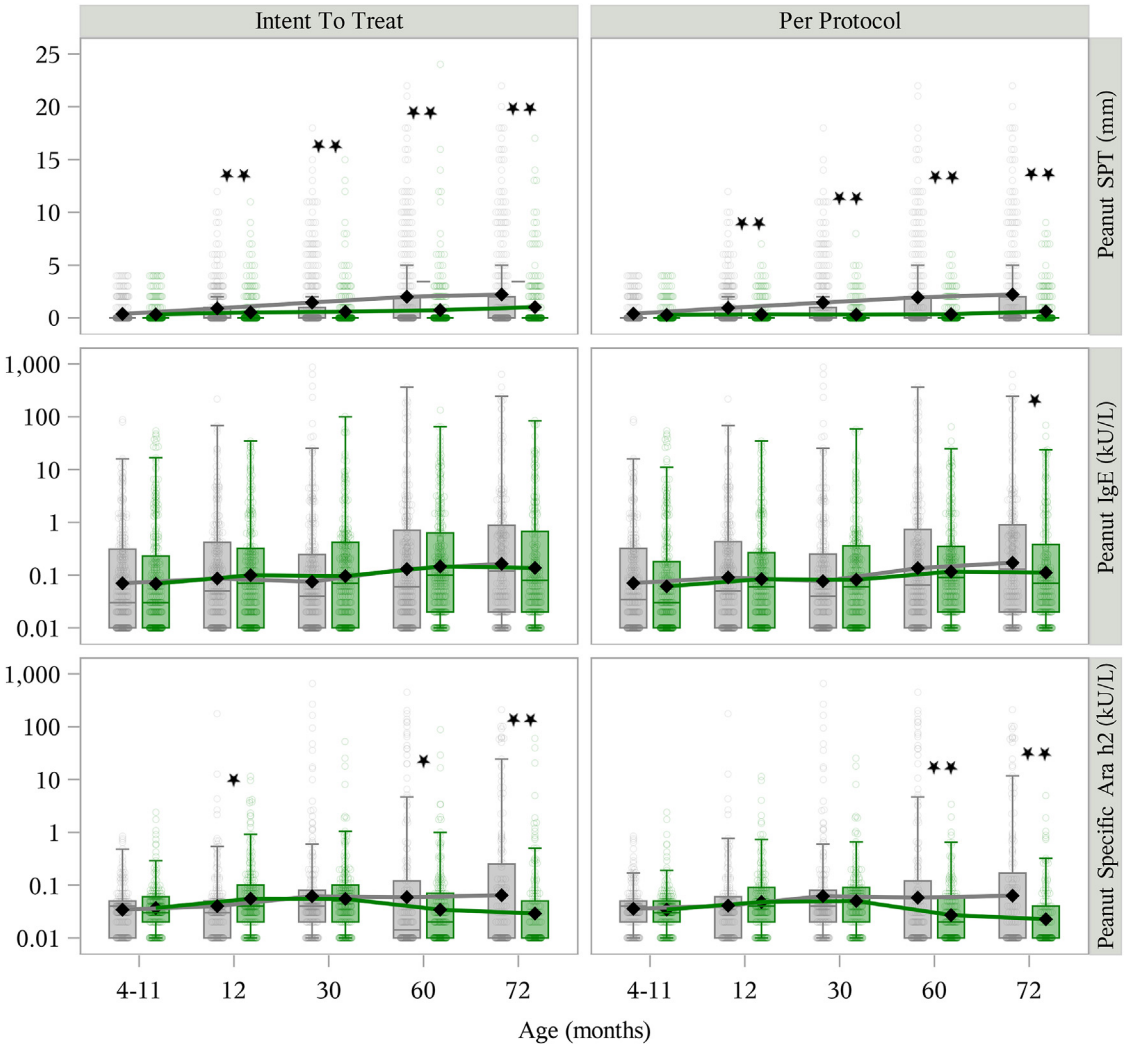

FIG 3. Peanut SPT responses, peanut-specific IgE levels, and Ara h 2–specific IgE levels. Peanut SPT responses *(top panel)*, peanut-specific IgE levels *(middle panel)*, and Ara h 2 IgE levels *(bottom panel)* in the consumption and avoidance groups in the ITT *(left column)* and LEAP PP *(right column)* populations at 4 to 11, 12, 30, 60, and 72 months are shown. *Boxes* represent 25th and 75th percentiles, and *error bars* represent 2.5th and 97.5th percentiles. Lines connect the means over time for each randomized group. *Solid gray lines* represent the LEAP avoiders. *Solid green lines* represent LEAP consumers. *Gray circles* represent LEAP avoiders. *Green circles* represent LEAP consumers. **P* value of .05 or less resulting from a comparison between the LEAP avoidance and LEAP consumption groups by using a 2-sample *t* test. ***P* value of .01 or less resulting from a comparison between the LEAP avoidance and LEAP consumption groups by using a 2-sample *t* test.

Eczema. The majority of participants in the ITT population had eczema (defined by a SCORAD score > 0) at baseline (97% in the avoidance group and 98% in the consumption group); this decreased across study time points to 72 months of age, with 39% of participants in the avoidance group and 37% in the consumption group having eczema (Fig 2). Overall, eczema severity (measured by mean SCORAD score) decreased across study time points from 34.4 (SD, 18.9) at baseline to 6.8 (SD, 11.2) at 72 months of age (after 12 months of peanut avoidance; see Table E3). There were no significant differences in the presence or severity of SCORAD scores between LEAP avoiders and consumers at any time point (Fig 2 and see Table E3). These findings were replicated in the PP population (see Table E4).

Asthma. In the ITT population the overall rate of asthma increased from 11.2% at 30 months to 16.5% at 60 months and 16.3% at 72 months of age (see Table E1). There were no significant differences in rates of asthma diagnosis or protocol-defined diagnostic criteria between the LEAP study avoiders and consumers at 30, 60, or 72 months of age (Fig 1 and see Table E1). These findings were replicated in the PP population (see Table E2).

Rhinoconjunctivitis. In the ITT population the overall rate of seasonal allergic rhinoconjunctivitis increased from 14.4% at 30 months to 35.2% at 60 months and 46.3% at 72 months of age (see Table E1). The rate of perennial allergic rhinoconjunctivitis increased from 26.4% at 30 months to 42.4% at 60 months and 51.8% at 72 months of age. Rates of seasonal and perennial allergic rhinoconjunctivitis were similar between LEAP study groups at 30, 60, and 72 months of age (Fig 1 and see Table E1). These findings were replicated in the PP population (see Table E2).

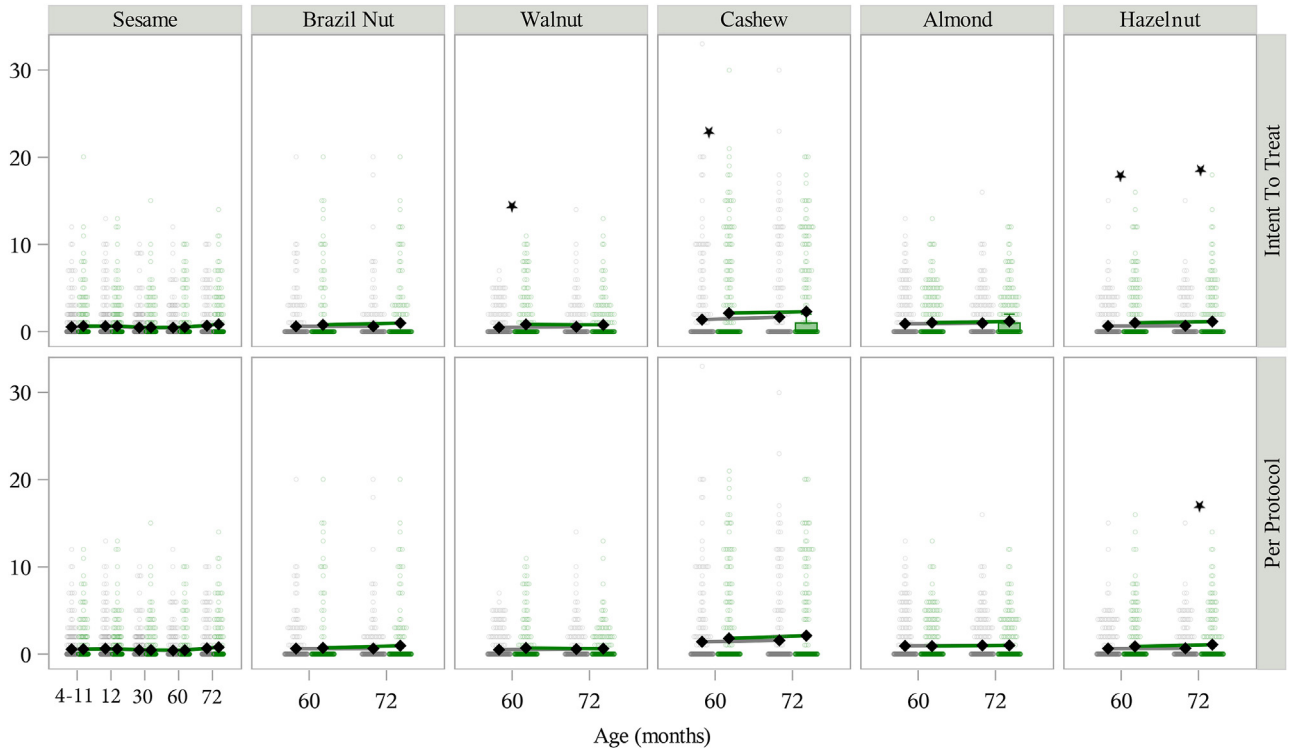

FIG 4. Tree nut and sesame SPT responses. Sesame, Brazil nut, walnut, cashew, almond, and hazelnut SPT responses (in millimeters) in the consumption and avoidance groups in the ITT *(top row)* and LEAP PP *(bottom row)* populations at 4 to 11, 12, 30, 60, and 72 months of age are shown for sesame and at 60 and 72 months of age for the other tree nut outcomes. *Boxes* represent 25th and 75th percentiles, and *error bars* represent 2.5th and 97.5th percentiles. Lines connect the means over time for each randomized group. *Solid gray lines* represent the LEAP avoiders. *Solid green lines* represent LEAP consumers. *Gray circles* represent LEAP avoiders. *Green circles* represent LEAP consumers. **P* value of .05 or less resulting from a comparison between the LEAP avoidance and LEAP consumption groups by using a 2-sample *t* test. ***P* value of .01 or less resulting from a comparison between the LEAP avoidance and LEAP consumption groups by using a 2-sample *t* test.

No protective effect on surrogate markers of tree nut and sesame allergy (SPT responses, specific IgE levels, and reported allergic reactions) in the LEAP study consumption group

We compared rates of sensitization to tree nut and sesame with those to peanut. As previously published for peanut, in the consumption group the mean peanut SPT wheal diameter was significantly lower at all time points after randomization in both the ITT and PP populations (Fig 3). In contrast, the mean peanut-specific IgE level was lower only in the consumption group at 1 time point at 72 months of age and lower only in the PP population (Fig 3). Mean Ara h 2 IgE levels were significantly lower in the consumption group at 60 and 72 months of age in both the ITT and PP populations (Fig 3).

For tree nuts and sesame, by using *a priori* sensitization levels (SPT wheal diameter ≥3 mm or specific IgE level ≥0.35 kU/L), the only significant difference noted was for walnut in the ITT population; the consumption group had an increased rate of walnut sensitization at 72 months compared with the avoidance group (28.2% vs 19.9%, $P = .025$; see Table E5 in this article's Online Repository at www.jacionline.org). This difference in walnut sensitization was not seen in the PP population (see Table E6 in this article's Online Repository at www.jacionline.org).

In *post hoc* analyses, by using higher cutoff levels (SPT wheal diameter ≥5 mm or specific IgE level ≥10 kU/L) as a marker of likely food allergy, there were significant increases in sensitization rates to hazelnut, cashew, and walnut in the consumption group in the ITT population (see Table E7 in this article's Online Repository at www.jacionline.org). These differences were largely attenuated in the PP population (see Table E8 in this article's Online Repository at www.jacionline.org). Considering sensitization based on SPT responses only, mean SPT wheal diameters to tree nuts and sesame were broadly similar between the consumption and avoidance groups in the ITT population. The exceptions were to walnut and cashew at 60 months and to hazelnut at 60 and 72 months, with mean wheal diameters being larger in the consumption group (Fig 4). In the PP population the only difference between groups was to hazelnut at 72 months of age (Fig 4). Considering sensitization by IgE only, in the ITT population mean specific IgE levels to tree nuts and sesame were generally similar between the consumption and avoidance groups; however, specific IgE levels were greater in the consumption group for some nuts at more than 1 time point (Fig 5). Most of these differences were not apparent in the PP population. Only for walnut in the ITT population were specific IgE levels greater in the consumption group at all time points after baseline. These

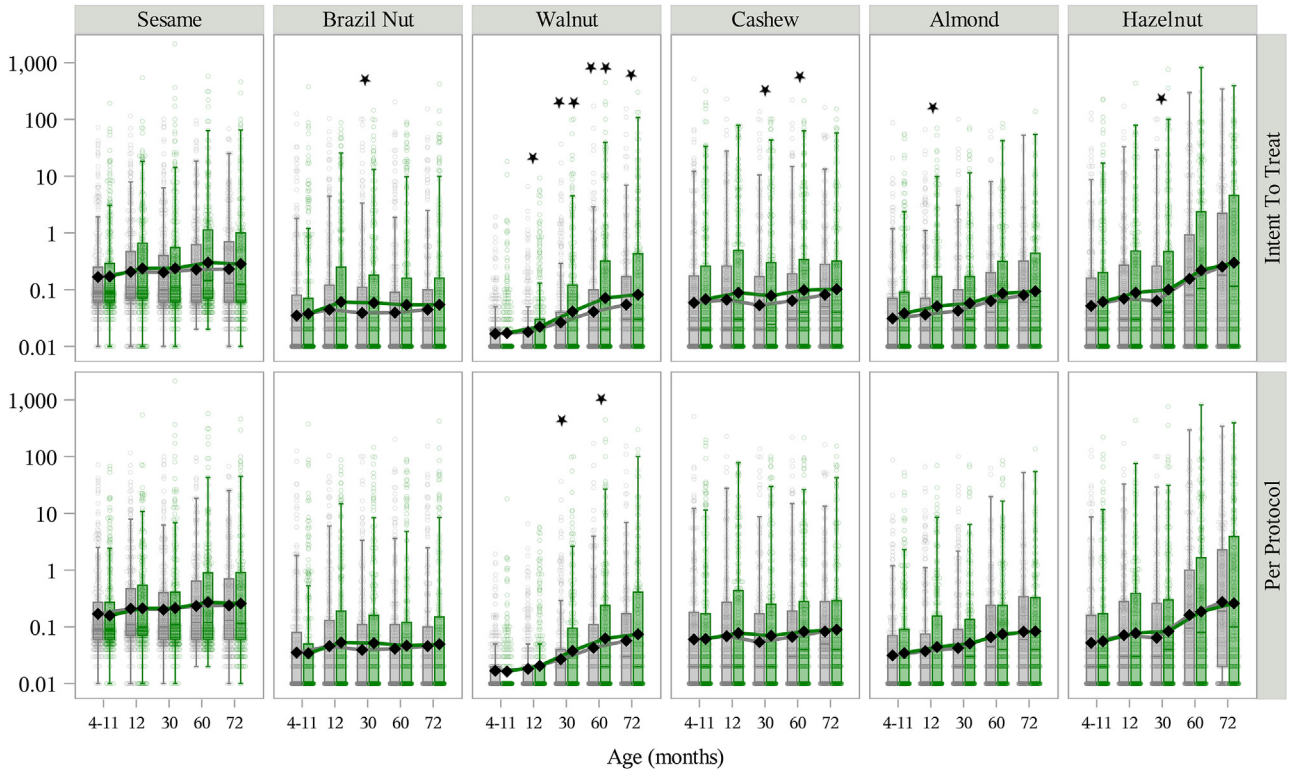

FIG 5. Tree nut– and sesame-specific IgE levels. Sesame-, Brazil nut–, walnut-, cashew-, almond-, and hazelnut-specific IgE levels (in kilounits per liter) in the consumption and avoidance groups in the ITT *(top row)* and LEAP PP *(bottom row)* populations at 4 to 11, 12, 30, 60, and 72 months are shown. *Boxes* represent 25th and 75th percentiles, and *error bars* represent 2.5th and 97.5th percentiles. Lines connect the means over time for each randomized group. *Solid gray lines* represent the LEAP avoiders. *Solid green lines* represent LEAP consumers. *Gray circles* represent LEAP avoiders. *Green circles* represent LEAP consumers. **P* value of .05 or less resulting from a comparison between the LEAP avoidance and LEAP consumption groups by using a 2-sample *t* test. ***P* value of .01 or less resulting from a comparison between the LEAP avoidance and LEAP consumption groups by using a 2-sample *t* test.

differences in walnut-specific IgE levels were also apparent in the PP population at 30 and 60 months of age.

When we compared reported reactions to tree nuts and sesame between the LEAP intervention groups, the only significant difference noted was for Brazil nut in the ITT population, where 5 participants in the consumption group reported Brazil nut reactions compared with 0 in the avoidance group ($P = .031$). A similar difference was noted for Brazil nut in the PP population (see Table E9 in this article's Online Repository at www.jacionline.org). Statistically significant differences were also noted when we compared the number of subjects reporting any or more than 1 reaction to tree nuts and sesame in both the ITT and PP populations (see Table E9). In the ITT population 40 (12.7%) participants in the consumption group reported a reaction to any nut compared with 23 (7.3%) participants in the avoidance group ($P = .023$). Most subjects who reported reactions to a tree nut also had specific IgE levels of 0.35 kU/L or greater to that nut. However, this was not the case in all subjects. For example, 10 of 26 subjects who reported a reaction to cashew did not have specific IgE levels of 0.35 kU/L or greater (see Table E10 in this article's Online Repository at www.jacionline.org).

To assess whether there were differences in consumption of tree nuts or sesame between groups, we compared the number of participants who reported ever eating tree nuts or sesame in 3-day food diaries (see Table E11 in this article's Online Repository at www.jacionline.org). The large majority of participants did not report consumption of tree nuts or sesame. Statistically significant differences were noted for hazelnuts and mixed nuts. For hazelnuts, 42 (13.2%) consumers reported eating hazelnut compared with 21 (6.5%) participants in the avoidance arm ($P = .005$). For mixed nuts, 5 participants in the consumption group reported mixed nut consumption compared with 0 in the avoidance group ($P = .030$).

No difference in rates and resolution of sensitization to other common foods between the LEAP intervention groups

There were no differences in rates of sensitization to cow's milk and egg white at any time point in the ITT (see Table E12 in this article's Online Repository at www.jacionline.org) or PP (see Table E13 in this article's Online Repository at www.jacionline.org) populations. No differences were noted in likely allergy rates by using high-level cutoffs of 5 mm or greater or 10 kU/L or greater for SPT responses and specific IgE measurements, respectively (see Tables E14 and E15 in this article's Online Repository at www.jacionline.org).

The high rate of raw egg white sensitization of 69.7% in the overall ITT population at baseline decreased with age to 39.1% by

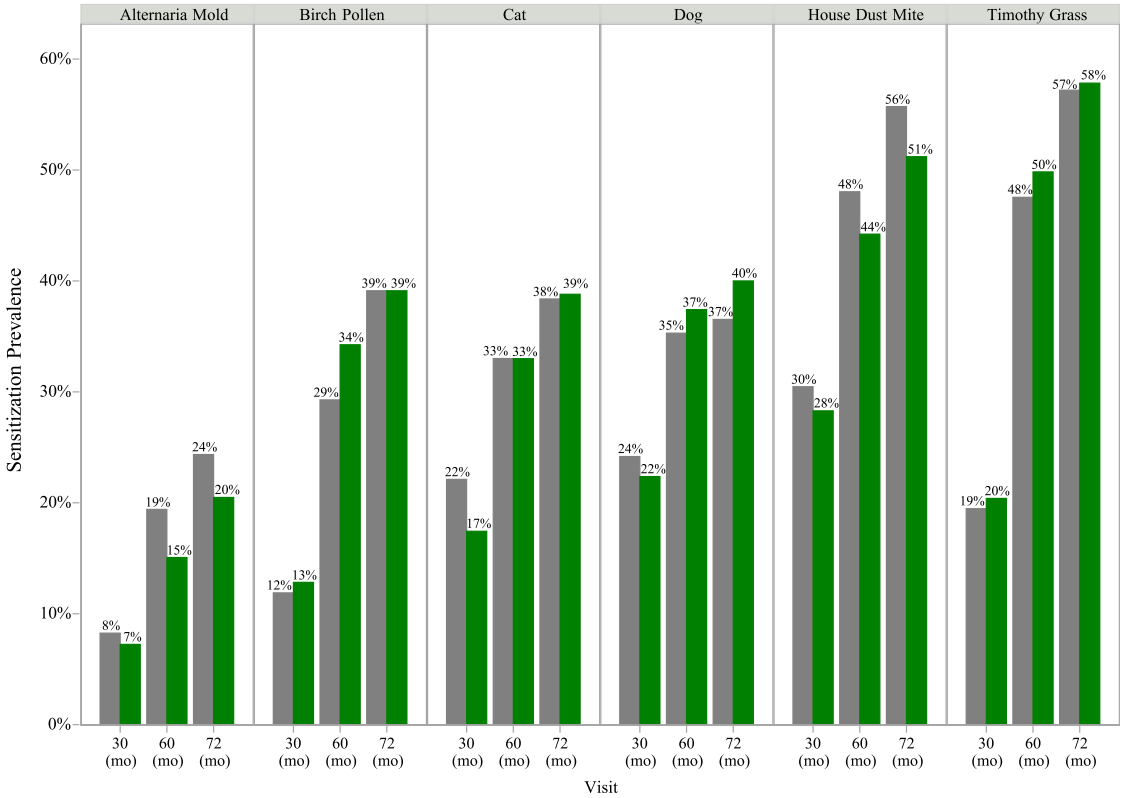

FIG 6. Aeroallergen sensitization. Prevalence of an IgE level of 0.35 kU/L or greater for several aeroallergens in the consumption *(green bars)* and avoidance *(gray bars)* groups at 30, 60, and 72 months of age are shown. There are no significant differences between the 2 groups at any time point, as assessed by using χ^2 tests.

72 months (see Table E12). A similar decrease was evident for the rate of SPT wheals of 3 mm or larger to egg white extract (see Table E12). Rates of soya sensitization and likely allergy in the ITT and PP populations were low and equivalent between LEAP groups at all measured time points (see Tables E12-E15 in this article's Online Repository at www.jacionline.org).

Increase in aeroallergen sensitization with age in both LEAP study intervention groups

Sensitization rates increased from 30 to 60 and 72 months of age for all aeroallergens (house dust mite, cat, dog, timothy grass pollen, birch pollen, and *Alternaria* species mold) in both the consumption and avoidance groups in the ITT (Fig 6 and see Table E16 in this article's Online Repository at www.jacionline.org) and PP (see Table E17 in this article's Online Repository at www.jacionline.org) populations. The most striking increase was for timothy grass pollen sensitization. In the ITT population the rate in the combined avoiders and consumers group increased from 19.9% at 30 months to 48.7% at 60 months and 57.5% at 72 months of age (see Table E16). There were no significant differences in aeroallergen sensitization between the consumption and avoidance groups at any time point (Fig 6 and see Table E16). These findings were replicated in the PP population (see Table E17).

Similar cumulative allergic disease burden in both LEAP study intervention groups

At 60 months of age, LEAP participants carried a high cumulative allergic disease burden, considering together eczema, asthma, rhinoconjunctivitis, or any likely food allergy defined as any food allergen SPT response of 5 mm or greater (Fig 7). The cumulative disease burden was not different between LEAP avoiders and consumers in the ITT population at 60 or 72 months of age (see Table E18 in this article's Online Repository at www.jacionline.org). When considering the cumulative disease burden in the combined avoiders and consumers group in the ITT population at 60 months of age, 76% of participants had at least 1 allergic disease (seasonal and perennial rhinoconjunctivitis, asthma, eczema, and likely food allergy) at 60 months, and 44% had multiple allergic diseases (Fig 7 and see Table E18).

Strong association between peanut allergy and allergic disease

We constructed 6 multivariate logistic regression models, including peanut allergy outcome, baseline egg allergy, and baseline SCORAD score, to assess their effect on the development of asthma, seasonal rhinoconjunctivitis, and perennial rhinoconjunctivitis separately at 60 and 72 months of age. Peanut allergy at 60 and 72 months was strongly associated with asthma, seasonal rhinoconjunctivitis, and perennial rhinoconjunctivitis in the ITT population at the same time point ($P < .001$ for the association of peanut allergy with all 3 allergic diseases at both time points, Fig 8 and see Table E19 in this article's Online Repository at www.jacionline.org). Similarly, baseline egg allergy was associated with seasonal ($P = .019$) and perennial ($P = .042$) rhinoconjunctivitis but not with asthma ($P = .848$) at 60 months of age. Similar findings were apparent at 72 months of age (Fig 8 and see Table E19). The association of

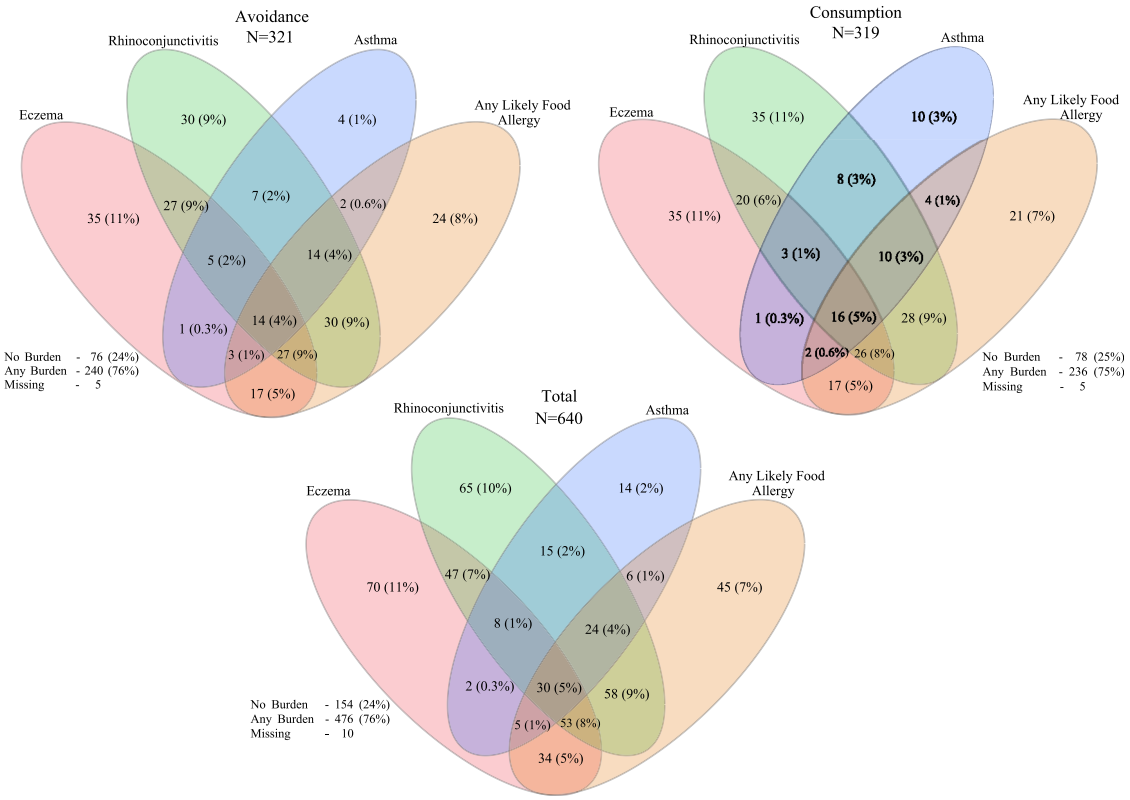

FIG 7. Cumulative burden Venn diagram at 60 months of age. Numbers of participants in the ITT population with protocol-defined eczema, rhinoconjunctivitis, asthma, or any likely food allergy are shown for the avoidance group *(top left)*, consumption group *(top right)*, and total study group *(bottom)*. This illustrates the very high rate of single and multiple allergic diseases in the study population. Figures are numbers (percentage) of participants.

asthma with peanut allergy, as opposed to its lack of association with egg allergy, is not explained by baseline SCORAD score because the latter does not influence the development of asthma (see Table E19).

DISCUSSION

This study found that oral tolerance induction to peanut in the LEAP study is specific for both allergen and allergic disease; that is, early consumption of peanut had no preventative effect on the development of asthma, allergic rhinoconjunctivitis, or surrogate markers of coexistent food allergies (SPT responses, specific IgE levels, and reported tree nut and sesame-induced reactions) and did not hasten the resolution of eczema or egg allergy, which were key inclusion criteria for LEAP study participation. The noted similarities in allergic disease burden between LEAP intervention groups is in contrast with the marked reduction in peanut allergy observed in the consumption group (see Fig E1 in this article's Online Repository at www.jacionline.org).

The allergen specificity of the LEAP intervention is confirmed by the finding that manifestations of allergic disease in the LEAP population followed the typical trajectory in young children, with no differences noted between groups (with the exception of peanut allergy in LEAP consumers). Sensitization to hen's egg white and cow's milk (see Tables E12-E15) and rates and severity of eczema decreased across all time points (see Tables E3 and E4). In contrast, we observed a significant increase in aeroallergen sensitization and both seasonal and perennial rhinoconjunctivitis across all measured time points (Figs 1 and 6). The burden of asthma was high and equal between LEAP groups, increasing from 11.2% at 30 months of age to 16.3% at 72 months of age (see Table E1).

When considering the association between peanut allergy, baseline egg allergy, and other allergic diseases, strong associations were noted with eczema and seasonal and perennial rhinoconjunctivitis at 60 and 72 months of age (Fig 8 and see Table E19). Peanut allergy was also strongly associated with asthma; this relationship was independent of baseline eczema, egg allergy, or both (Fig 8). The LEAP study demonstrated that peanut consumption was strongly associated with the prevention of peanut allergy but did not prevent asthma (see Fig E1). Therefore the environmental and genetic risk factors for asthma and peanut allergy are likely distinct.

There was no evidence that peanut consumption protected against tree nut and sesame sensitization. Surprisingly, there was a small signal that peanut consumption was associated with an increase in sensitization to tree nuts and sesame. We found higher SPT responses and specific IgE levels to tree nuts and sesame in the LEAP consumption group compared with the avoidance group at most time points, and at times, these differences met statistical significance. In addition, a significantly higher proportion of subjects ($P = .023$) in the consumption group reported an allergic reaction to 1 or more tree nuts. These findings contrast with the LEAP study findings at 60 months of age, with challenge-proved peanut allergy, peanut SPT

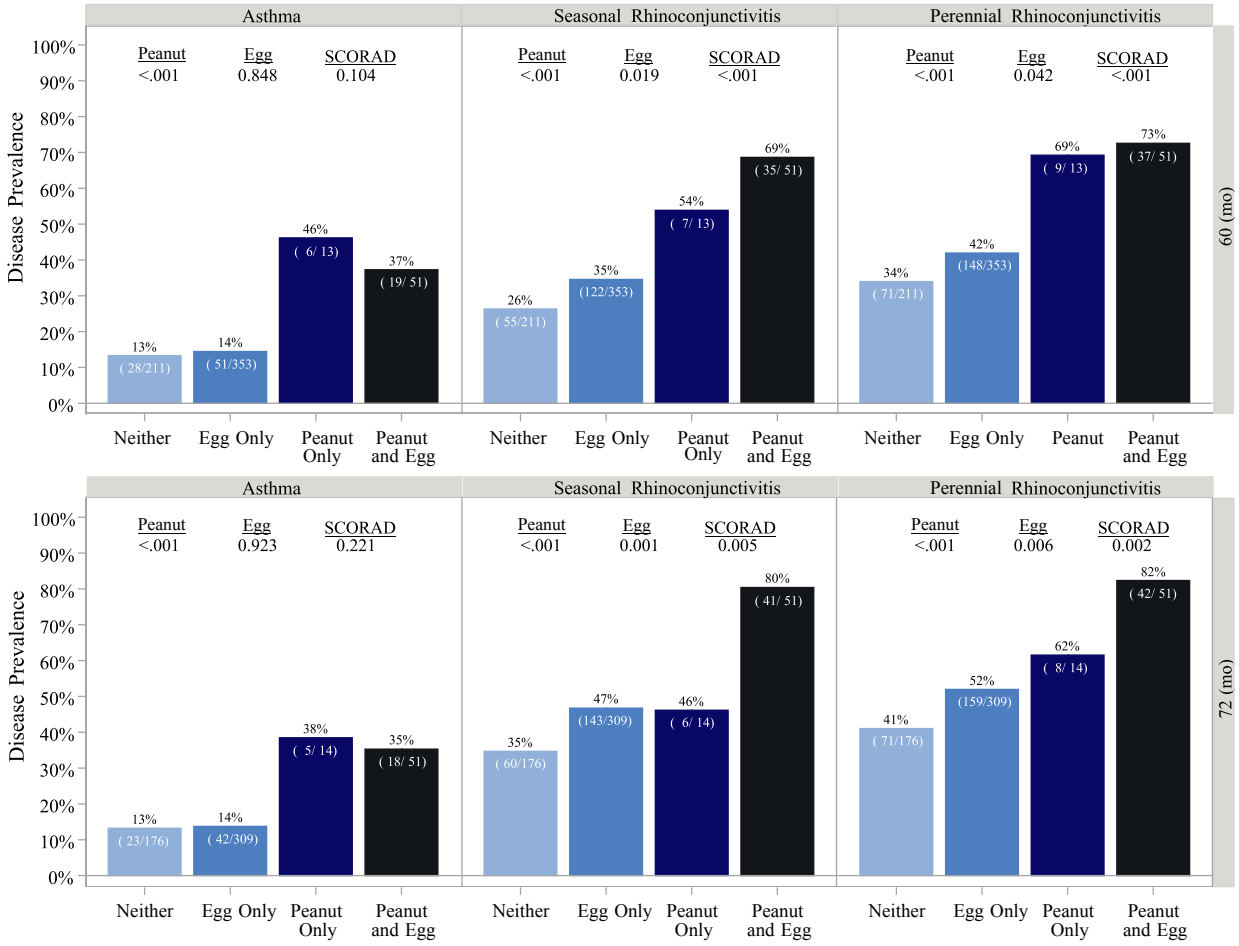

FIG 8. Peanut and egg allergy associations with development of allergic diseases. Rates of protocol-defined asthma *(left)*, seasonal rhinoconjunctivitis *(middle)*, and perennial rhinoconjunctivitis *(right)* at 60 *(top)* and 72 *(bottom)* months are shown in those with neither egg nor peanut allergy, egg allergy only, peanut allergy only, or both egg and peanut allergy. The number of subjects contributing to each group is presented in the denominator, and the number of subjects with each allergic disease within each group is presented in the numerator of the values annotated within each bar. Presence of egg allergy was defined per inclusion criteria at baseline, whereas peanut allergy was defined at 60 and 72 months. *P* values resulting from a multivariate logistic regression model (outcome of interest being each allergic disease) adjusted for peanut allergy, baseline egg allergy, and baseline SCORAD score are annotated within each panel.

diameters, and Ara h 2 levels (Fig 3) all reduced markedly within the LEAP consumption group compared with the avoidance group.

It is possible that early peanut consumption resulted in the slightly increased rate of sensitization to tree nuts and could potentially result from exposure to small quantities of epitopes cross-reactive with those of tree nuts. There is literature to suggest that low-level allergen exposure (to aeroallergens) results in allergic responses, whereas high-level allergen exposure drives tolerance.[20,21] In addition, subjects in the consumption group might have had levels of exposure to tree nuts potentially sufficient to drive sensitization but insufficient to induce tolerance.

However, there are a number of other explanations for these unexpected findings. First, the increase in tree nut sensitization observed in the consumption group was not statistically consistent over time in that the effect sizes were smaller and more variable compared with peanut.

Second, to minimize false-negative results, no adjustments were made for multiple comparisons, which increases the likelihood of false-positive findings.

Third, if eating peanut causes an increase in tree nut sensitization and reported allergic reactions, we would expect to see a greater effect in the PP analyses, in which infants ate more peanut compared to the ITT analyses; however, this was not evident for either the *a priori* sensitization thresholds (compare Tables E5 and E6) or the high-level sensitization thresholds that are more indicative of clinical allergy. This suggests that these small and statistically significant differences in sensitization do not represent important clinical differences (compare Tables E7 and E8).

Fourth, differences in reported allergic reactions can arise through an ascertainment bias as a consequence of increased exposure to tree nuts and sesame in participants randomized to peanut consumption (see Table E9). In support of this, consumption data recorded in 3-day food diaries suggest more frequent consumption in the LEAP consumption group (see Table E11). In addition, this method might underestimate differences in consumption patterns compared with a food frequency questionnaire (as was used to record both frequency and quantity of peanut consumption in LEAP participants).

Finally, although there was overall a significant increase in reported reactions to tree nuts and sesame in the consumers compared with avoiders, between only 20% and 50% of subjects with a reported reaction had specific IgE levels of 0.35 kU/L or greater to the reported nut, which suggests that some reported reactions do not represent true allergic reactions (see Table E10).

In contrast to allergy and dietary data in Israel, where higher and more frequent peanut consumption patterns are associated with low rates of reported tree nut and sesame allergy, we demonstrate that peanut consumption in the LEAP study does not protect against tree nut and sesame allergy, and furthermore, our data raise the possibility that peanut consumption can cause sensitization to tree nuts.[14,15] However, in the absence of oral food challenges to tree nuts and sesame, the clinical significance of these small and inconsistent differences in surrogate markers of food allergy remains unclear. The LEAP Trio study will make a more detailed assessment of these differences at age 10 years.

A strength of this study is that we describe secondary allergy outcomes for eczema, asthma, and seasonal and perennial rhinoconjunctivitis using rigorous *a priori* criteria in a population of infants with a high allergic disease burden and for which peanut consumption successfully reduced the rate of peanut allergy. The major limitation of this study is the absence of OFCs to tree nuts and sesame. An additional limitation is that severe eczema, egg allergy, or both served as enrollment criteria, thereby minimizing the opportunity to assess peanut consumption as an intervention to prevent the onset of these allergic conditions.

Despite the dramatic decrease in peanut allergy in participants randomized to peanut consumption, the overall allergic disease burden in LEAP study participants is high but equivalent between LEAP groups at 60 and 72 months of age (after 12 months of peanut avoidance). This demonstrates that oral tolerance induction to peanut in the LEAP study is specific for both allergen and allergic disease. The underlying immune mechanisms associated with tolerance to peanut do not alter the natural history of allergic disease. Different prevention strategies or strategies that include multiple dietary interventions need to be tested to assess whether the reduction in peanut allergy observed in the LEAP consumption group can be extended to other common food allergens and allergic diseases.

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Key messages

- **Prevention of peanut allergy through early peanut consumption is allergen specific and allergic disease specific.**
- **The immune mechanisms underlying tolerance to peanut do not hasten resolution of other allergic disease.**

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